REMARKS

This Reply is responsive to the Office Action dated February 25, 2003. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.116 is respectfully requested.

I. Status of the Claims

Claims 1-21, 50-52, 55-59 and 62-65 continue to be pending and under examination. Applicants acknowledge with appreciation the indication in the Office Action (page 5) that claim 1 is allowed.

II. Amendments to the Claims

Claim 51 was amended above to separate "growth/differentiation factors" into the separate terms "growth factors" and "differentiation factors," as suggested in the Office Action at page 5. Claim 52 was amended above to correct an inadvertent spelling error introduced in the amendment filed December 4, 2002. And claim 59 was amended to indicate that the recited Flp transgene in step (c) is a Flp "recombinase" transgene, as suggested in the Office Action at page 5.

No prohibited new matter was added by any of these amendments.

III. Rejection under 35 U.S.C. §112, first paragraph, enablement

Claims 2-51, 55-58 and 62-65 remain rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a FLP recombinase transgene under the control of a tissue-specific promoter

and the reporter gene under control of a non-tissue-specific (ubiquitous) promoter wherein the reporter gene comprises a disruption of two FLP recognition sequences in direct repeat orientation such that the reporter gene produces active product only when in the recombined form, allegedly fails to provide enablement for transgenic mice as broadly as claimed. Further, according to the rejection (page 3 of the Office Action), the claims "must be congruent with the asserted utility of the invention, which in the instant case is cell fate mapping . . . However, the claims remain broader than the scope of enablement."

At the outset, Applicants respectfully note that claim 59 is specifically directed to the embodiment of cell fate mapping. Further, claim 59 has not been included in the rejection under §112, first paragraph. Claim 59 is therefore "congruent" with the asserted utility of cell fate mapping and is fully enabled, as it has not been included in the rejection and it is specifically directed to a method of cell fate mapping.

Claims 62-65 are dependent on claim 59 and are therefore also directed to methods of cell fate mapping. Further, claims 62-65 are more narrow in scope than claim 59. Claims 62-65 should therefore also be enabled for their full scope, since claim 59 was not included in the rejection and is enabled for its full scope.

The Examiner notes in the Office Action (at the bottom of page 3) that the suggestion that claims that are more narrow than an enabled claim automatically makes them enabled is incorrect, as a broad claim is permitted to cover a vast number of inoperative embodiments. However, the Examiner has not provided any explanation why the invention recited in claims 62-65 would be inoperative. Claim 62 merely recites different known histochemical markers that may be used to detect FLP recombinase

activity in cells expressing the FLP recombinase transgene as recited in claim 59. Absent some reasoning why these specific markers would not be expected to be operative in the cell fate mapping method recited in claim 59, claim 62 should also be enabled for its full scope.

Likewise, claim 63 merely recites that the detectable product of claim 59 is a transcript that is detected by *in situ* hybridization. *In situ* hybridization of mRNA transcripts is a common method of detecting gene expression that is known in the art. Absent some explanation why this technique could not be used to detect FLP recombinase activity in the method of claim 59, claim 63 should also be enabled for its full scope.

Claim 64 recites that the detectable product of claim 59 is a peptide tag that is detectable by binding to a cognate binder. This type of structural interaction is a common method for detecting expression of a specific protein that is known in the art. Absent some explanation why this technique could not be used to detect FLP recombinase activity in the method of claim 59, claim 65 should also be enabled for its full scope.

Claim 65 recites different peptide tag and cognate binder pairs that are known in the art. Absent some explanation why any one of these known binding pairs could not be used to detect FLP recombinase activity in the method of claim 59, claim 65 should also be enabled for its full scope.

Thus, given that claim 59 is enabled and claims 62-65 merely recite known methods of detecting gene expression that may be used in the method of claim 59, claims 62-65 should also be enabled. If the rejection of claims 62-65 is maintained, then Applicants request that the Examiner provide reasoning as to why the specific markers

recited in claim 62, and the hybridization method recited in claim 63, and the peptide tag and cognate binder detection methods recited in claims 64 and 65, would be expected to be inoperative.

Claim 52 is directed to a transgenic mouse comprising a Flp recombinase transgene integrated into the genome of the transgenic mouse, wherein the Flp recombinase transgene is expressed from a tissue specific or a developmental stage specific promoter in at least one cell of the transgenic mouse at a level sufficient to catalyze recombination between two FLP-recognition sequences in direct repeat orientation in said cell, wherein said recombination is detected by activation of a gene expressed from a ubiquitous promoter, wherein said gene produces a detectable product only when in recombined form. Claim 52 was not included in the enablement rejection. Claim 52 is therefore fully enabled, especially since the Office Action states that the specification is enabling for "a transgenic mouse comprising a FLP recombinase transgene under the control of a tissue-specific promoter and the reporter gene under control of a non-tissue-specific (ubiquitous) promoter wherein the reporter gene comprises a disruption of two FLP recognition sequences in direct repeat orientation such that the reporter gene produces active product only when in the recombined form" (see page 2 of the Office Action).

Claims 55-58 are dependent on claim 52 and are therefore also directed to a transgenic mouse having the characteristics recited above. Further, claims 55-58 are more narrow in scope than claim 52. Claims 55-58 should therefore also be enabled for their full scope, since claim 52 was not included in the rejection and is enabled for its full scope.

The Examiner notes in the Office Action (at the bottom of page 3) that the suggestion that claims that are more narrow than an enabled claim automatically makes them enabled is incorrect, as a broad claim is permitted to cover a vast number of inoperative embodiments. However, the Examiner has not provided any explanation why the invention recited in claims 55-58 would be inoperative. Like claim 62 discussed above, claim 55 merely recites different known histochemical markers that may be used to detect FLP recombinase activity in cells expressing the FLP recombinase transgene as recited in claim 52. Absent some reasoning why these specific markers would not be expected to be operative in the transgenic mouse recited in claim 52, claim 55 should also be enabled for its full scope.

Likewise, as noted for claim 63 above, claim 56 merely recites that the detectable product of claim 52 is a transcript that may be detected by *in situ* hybridization. *In situ* hybridization of mRNA transcripts is a common method of detecting gene expression that is known in the art. Absent some explanation why this technique could not be used to detect FLP recombinase activity in the transgenic mouse of claim 52, claim 56 should also be enabled for its full scope.

Like claim 64 discussed above, claim 57 recites that the detectable product in claim 52 is a peptide tag that is detectable by binding to a cognate binder. This type of structural interaction is a common method for detecting expression of a specific protein that is known in the art. Absent some explanation why this technique could not be used to detect FLP recombinase activity in the transgenic mouse of claim 52, claim 57 should also be enabled for its full scope.

Like claim 65 discussed above, claim 58 recites different peptide tag and cognate binder pairs that are known in the art. Absent some explanation why any one of these known binding pairs could not be used to detect FLP recombinase activity in the transgenic mouse of claim 52, claim 58 should also be enabled for its full scope.

Thus, given that claim 52 is enabled and claims 55-58 merely recite known methods of detecting gene expression that may be used in the transgenic mouse of claim 52, claims 55-58 should also be enabled. If the rejection of claims 55-58 is maintained, then Applicants request that the Examiner provide reasoning as to why the specific markers recited in claim 55, and the hybridization technique recited in claim 56, and the peptide tag and cognate binder detection techniques recited in claims 57 and 58, would be expected to be inoperative.

Claim 1 is directed to a transgenic mouse comprising a FLP recombinase transgene under control of a tissue-specific promoter integrated in a genome of the transgenic mouse, wherein the Flp recombinase transgene is expressed in a cell of the transgenic mouse at a level of recombinase activity sufficient to catalyze recombination between Flp-recognition sequences. Claim 1 was not included in the enablement rejection and is therefore fully enabled. Further, claim 1 has been found to be allowable (see Office Action, page 5).

Applicants questioned in the Reply filed December 4, 2002, how a broad claim could be found to be enabled, whereas claims that are more narrow and dependent on that broad claim could be rejected for enablement under §112, first paragraph. The Examiner responded by noting in the Office Action (at the bottom of page 3) that claims that are more narrow than an enabled claim are not automatically enabled, because a broad claim

is permitted to cover a vast number of inoperative embodiments. While the Examiner is correct to note that inoperative embodiments may be encompassed by a broad claim, the Examiner has not provided any explanation why every invention recited in claims 2-21, 50 and 51 would be inoperative.

Claim 2 is dependent on allowed claim 1 and merely states that the transgenic mouse of claim 1 further comprises a FLP recognition sequence. Claim 3 is directed to two specific FLP recognition sequences disclosed in the specification. Claim 6 states that the genome comprises at least two FLP recognition sequences. It is not clear why a transgenic mouse that is fully enabled for the expression of a Flp recombinase transgene in a cell at a level of recombinase activity sufficient to catalyze recombination between Flp-recognition sequences would not be enabled or operative when it also contains a FLP recognition sequence, or more specifically, the FLP recognition sequences disclosed in the specification.

Claim 4 is directed to the transgenic mouse of claim 2 where the mouse contains at least two diploid cells with different numbers of FLP recognition sequences. The specification discloses at the paragraph bridging pages 4-5 that a chimeric or mosaic transgenic mammal may contain cells with different numbers of FLP recognition sequences due to Flp-mediated recombination. For instance, a cell in which recombination has not taken place may contain two FLP recognition sequences, whereas a cell in which recombination has taken place may contain only one. It is not clear why the transgenic mouse recited in claim 4 is any less enabled than the transgenic mouse recited in claim 1, particularly given the Examiner's emphasis on the cell fate mapping embodiment in which a transgenic mammal would be expected to contain cells with

different numbers of FLP recognition sequences depending on which cells developed along the path resulting in Flp recombinase activity.

Claim 5 is directed to the transgenic mouse of claim 2 wherein the genome is hemizygous for the FLP recognition sequence. According to the specification at page 5, first paragraph, a genome is hemizygous for the FLP recognition sequence when the recognition sequence is integrated on only one pair of homologous chromosomes. It is not clear why the transgenic mouse of claim 1 is enabled whereas the mouse of claim 5 is not, particularly when it is common practice to create both hemizygous and homozygous transgenic mice by breeding techniques.

Claim 7 is directed to the transgenic mouse of claim 6, wherein the genome comprises at least two chromosomes, each chromosome comprising a FLP recognition sequence. According to the specification at page 5, first full paragraph, recombination between two FLP recognition sequences located on different chromosomes may be used to create a translocation between those chromosomes, and that translocations are commonly used to create mutations that lead to developmental abnormalities. Thus, it is not clear why the mouse of claim 1 is enabled and the mouse of claim 7 is not, particularly when claim 7 is merely more specific than claim 1 as to the location of the FLP recognition sequences.

Claim 8 is dependent on allowed claim 1 and states that the genome of the transgenic mouse further comprises two FLP recognition sequences in direct repeat orientation. The Office Action specifically states at page 2 that the specification is enabling for a transgenic mouse comprising two FLP recognition sequences in direct repeat orientation. It is not clear, then, why claim 1 has been found to be allowable and

claim 8 has been rejected for lack of enablement, particularly when the Office Action states that the specification is enabling for a mouse with the characteristic recited in claim 8.

Claim 9 is dependent on claim 1 and states that the genome of the transgenic mouse comprises two FLP recognition sequences in inverted repeat orientation. According to the specification at page 5, third full paragraph, inverted repeat FLP recognition sequences may be used to cause inversion of an intervening sequence or gene, which may cause activation or inactivation of a gene. In particular, the specification discloses that this is one method of tracing cell lineages, or performing cell fate mapping, which has already been found to be enabled (Office Action, page 3). Thus, it is not clear why the transgenic mouse of claim 1 is enabled but the mouse of claim 9 is not, particularly when claim 9 merely specifies the orientation of the FLP recognition sequences, and the specification discloses that FLP recognition sites oriented in this particular manner may be used to perform cell fate mapping.

Claim 10 merely recites that the transgenic mouse of claim 1 further comprises a Cre transgene. According to the Background of the specification at page 1, Cre-mediated recombination had been successfully used in transgenic mice at the time the present invention was made. Absent some evidence or reasoning as to why the transgenic mouse of claim 1 would become inoperative if it also contained a Cre transgene, claim 10 should also be enabled by the specification.

Claim 12 is dependent on claim 1 and specifies that the genome further comprises another transgene that is flanked by FLP recognition sequences. Claim 11 specifies that a drug selectable marker in particular is flanked by FLP recognition sequences, and that the

drug marker is excised in cells containing sufficient recombinase activity. According to the specification, inactivation of a selectable marker is one way in which cell lineages may be traced, or cell fates may be mapped (page 5, third full paragraph). Again, cell fate mapping is an embodiment that the Office Action has already found to be enabled. Absent some evidence or explanation as to why inactivation of a selectable marker could not be used to perform cell fate mapping, it is not clear why claims 11 and 12 would not be enabled.

Claim 15 further defines the other transgene of claim 12 as being selected from the group consisting of genes controlling differentiation of a cell or development of an organism, genes required for viability, cytokine genes, neurotransmitter or neurotransmitter receptor genes, oncogenes, tumor suppressor genes, selectable markers and histochemical markers. Claim 51 is dependent on claim 15 and further defines specific types of genes controlling differentiation or development. Absent some evidence or explanation as to why these specific types of genes would render the claimed transgenic mouse inoperable when they are flanked by FLP recognition sequences, it is not clear why claim 1 is enabled whereas claims 15 and 51 are not enabled.

Claims 13 and 16 specify that the other transgene is flanked by direct repeat FLP recognition sequences, whereas claims 14 and 17 specify that the flanking FLP sequences are in inverted repeat orientation. Again, the Office Action has already acknowledged that the specification is enabling for recognition sequences in direct repeat orientation. Furthermore, the specification discloses that FLP recognition sequences in the inverted repeat orientation may be used to perform cell fate mapping, an embodiment that the Office Action has already recognized to be enabled by the specification. Thus, absent

evidence why a transgene between the FLP recognition sequences would render the transgenic mouse inoperative, it is not clear why claims 13, 14, 16 and 17 are not enabled.

Claim 18 is dependent on claim 12 and further specifies that expression of the additional transgene is activated in cells containing sufficient Flp recombinase activity. Claim 19 is dependent on claim 12 and further specifies that expression of the additional transgene is inactivated in cells containing sufficient Flp recombinase activity. According to the specification at page 5, paragraphs 2 and 3, a sequence or gene between two FLP recognition sequences may be activated or inactivated by Flp recombinase activity. It is not clear why both of these embodiments would be considered to be inoperative when the broader concept of expressing Flp recombinase activity in a cell at a level sufficient to cause recombination between FLP recognition sequences, as recited in claim 1, is enabled.

Claim 20 is dependent on claim 1 and specifies that FLP recombinase activity is regulated by a factor selected from the group consisting of chemical, developmental stage or temperature. These are common environmental stimuli known in the art to activate the expression of specific genes. In fact, placing the expression of the Flp recombinase gene under control of a developmentally regulated promoter can be used to assess the effect of gene expression in a subset of cells, or to activate or inactivate a lineage tracer in populations of cells and their descendants so that cell lineages can be identified and functionally characterized (see specification at the paragraph bridging pages 12-13). Absent some evidence or explanation why such environmental stimuli could not be used to control Flp recombinase transgene expression, it is not clear why claim 20 would not

be enabled whereas the cell fate mapping embodiment of the invention is enabled, as is the mouse of claim 1.

Claim 21 is dependent on claim 1 and further defines the Flp recombinase transgenes as encoding specific amino acid sequences disclosed in the specification. Absent some evidence why these specific amino acid sequences would be inoperative, there has been no reason advanced as to why the mouse of claim 1 would be enabled but the mouse of claim 21 would not.

Claim 50 is dependent on claim 12 and further specifies that transcription of the other transgene is under control of a regulatory region from a gene selected from a specified group of genes. It is not clear why placing the other transgene in the cell under the control of any specific promoter would render the transgenic mouse of the claimed invention inoperable.

Thus, given that claim 1 is enabled and claims 2-21, 50 and 51 merely recite specific positions of FLP recognition sequences in the cell, other transgenes that may be included, and known methods of regulating the expression of the Flp recombinase transgene that may be used in the transgenic mouse of claim 1, claims 2-21, 50 and 51 should also be enabled. If the rejection of claims 2-21, 50 and 51 is maintained, then Applicants request that the Examiner provide reasoning as to why the specific FLP recognition sequence positions, other transgenes and known methods of regulating gene expression as recited in these dependent claims would be expected to be inoperative when used in the transgenic mouse of claim 1.

In view of all the remarks provided above, reconsideration and withdrawal of the rejection under §112, first paragraph, are respectfully requested.

IV. Rejections under 35 U.S.C. §112, second paragraph

Claim 51 remains rejected under §112, second paragraph, because the phrase "growth/differentiation factors" is allegedly unclear. The Examiner noted Applicants' previous Reply filed December 4, 2002, which discusses a variety of growth factors and differentiation factors, but pointed out that the claim recites "growth/differentiation factors" rather than growth factors *and* differentiation factors. Applicants believe that the amendment to claim 51 presented above resolves this rejection.

Claim 52 was rejected under §112, second paragraph, because it included an inadvertent typographical error. Applicants believe that the amendment to claim 52 presented above resolves this rejection.

Finally, claim 59 was rejected under §112, second paragraph because it recites a "FLP transgene" in step (c) rather than a FLP *recombinase* transgene. Applicants believe that the amendment to claim 59 presented above resolves this rejection.

In view of the amendments and remarks above, reconsideration and withdrawal of the rejections under §112, second paragraph, are respectfully requested.

This reply is fully responsive to the Office Action dated February 25, 2003. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit

Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted

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APPENDIX

The following amendments were entered above:

IN THE CLAIMS

51. (Three Times Amended) The transgenic mouse according to claim 15, wherein said another transgene is a gene controlling differentiation of a cell or development of an organism selected from the group consisting of genes encoding adhesion molecules, cyclin kinase inhibitors, Wnt family members, Pax family members, Winged helix family members, Hox family members, cytokines, interleukins, growth[/] factors, differentiation factors and their receptors, kinases, phosphatases, metabolic enzymes, and antigen receptors.

52. (Twice Amended) A transgenic mouse comprising a Flp recombinase transgene [intergrated] integrated into the genome of the transgenic mouse, wherein the Flp recombinase transgene is expressed from a tissue specific or a developmental stage specific promoter in at least one cell of the transgenic mouse at a level sufficient to catalyze recombination between two FLP-recognition sequences in direct repeat orientation in said cell, wherein said recombination is detected by activation of a gene expressed from a ubiquitous promoter, wherein said gene produces a detectable product only when in recombined form.

59. (Twice Amended) A method of mapping the developmental fate of a cell *in vivo* comprising:

(d) providing a transgenic mouse comprising a genome which contains a Flp recombinase transgene under control of a tissue-specific or developmental stage specific promoter and at least two FLP recognition sequences in direct orientation;

(e) expressing the Flp recombinase transgene at a level sufficient to catalyze site-specific recombination between said FLP recognition sequences in at least one cell; and

(f) detecting said recombination in said at least one cell by detecting activation of a gene expressed from a ubiquitous promoter, wherein said gene produces a detectable product only when in recombined form, and wherein said recombination is evidence of expression of said Flp recombinase transgene in said cell or a developmental precursor to said cell.